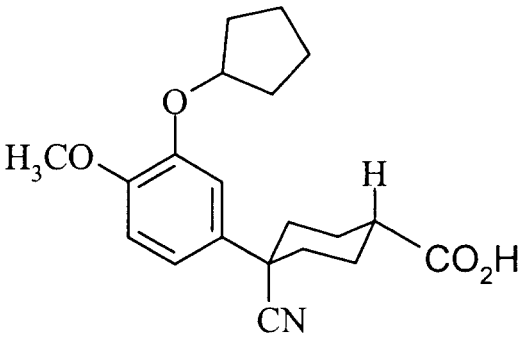
PRESCRIBING INFORMATION

ARIFLO®
(cilomilast)
Tablets

DESCRIPTION

ARIFLO Tablets contain cilomilast, an orally active, synthetic, selective phosphodiesterase-4 (PDE4) inhibitor. Cilomilast is chemically designated as *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexanecarboxylic acid, and it has the following structure:



The molecular formula is $C_{20}H_{25}NO_4$, representing a molecular weight of 343.4.

Cilomilast is a white to off-white crystalline powder with a pKa of 4.58. It is practically insoluble (<0.01 mg/mL) in acid media. The solubility increases rapidly above a pH of 6 and is >1 mg/mL at a pH of 7 and above.

Each ARIFLO Tablet for oral administration contains 15 mg of cilomilast. Each tablet also contains the inactive ingredients FD&C Blue No. 2 Aluminum Lake, hypromellose, lactose monohydrate, magnesium stearate, magrogol 400, microcrystalline cellulose, sodium starch glycolate, synthetic red iron oxide, synthetic yellow iron oxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: Cilomilast selectively inhibits the PDE-4 isoenzyme and is essentially devoid of activity at other PDE isozymes. By inhibiting the PDE-4 isoenzyme, cilomilast prevents the breakdown of cyclic 3',5'-adenosine monophosphate (cAMP), a second messenger that suppresses inflammatory cell function and mediates airway smooth muscle relaxation. Cilomilast may exert its therapeutic effects in patients with chronic obstructive pulmonary disease (COPD) by modulating these processes.

In preclinical studies, cilomilast promoted airway smooth muscle relaxation, inhibited immune and inflammatory cell activation, and inhibited cellular infiltration and mediator (histamine, tumor necrosis factor) release. Cilomilast may also modulate neuronal control of bronchoconstriction by inhibiting tachykinin activity via potentiation of non-adrenergic, non-cholinergic transmission.

In vitro, cilomilast induced a concentration-dependent suppression of the activity of various immune and inflammatory cells, including eosinophils, neutrophils, basophils, and T-cells. Cilomilast also inhibited inflammatory cell trafficking of both neutrophils and CD8+ T cells in in vivo studies. In a 12-week study in patients with COPD, there was no reduction in sputum neutrophils, but a reduction in sub-epithelial macrophages (CD68+) was noted.

Pharmacokinetics: ***Absorption:*** Cilomilast is rapidly absorbed following oral administration in the fasted state (median T_{max} 1.8 hours), and has an absolute bioavailability close to 100%. The pharmacokinetics of cilomilast after morning and evening dosing are comparable.

Cilomilast exhibits linear pharmacokinetics in healthy volunteers, with dose-proportional increases in exposure (C_{max} and AUC) following single (0.2 to 20 mg) and repeat (2 to 30 mg twice daily) dosing. Pharmacokinetic steady state is reached within 2 days of twice-daily dosing, as predicted from the average cilomilast elimination half-life of 7 to 8 hours. Cilomilast $AUC_{(0-12)}$ at steady state was comparable to single-dose $AUC_{(0-\infty)}$, indicating predictable pharmacokinetics upon repeat dosing.

Food Effects: Systemic exposure, as assessed by $AUC_{(0-\infty)}$, was unchanged following administration of ARIFLO after a high-fat meal compared to fasted dosing, but the rate of absorption was decreased (median T_{max} 4 hours), resulting in an average 39% reduction in C_{max}.

Distribution: Intravenous studies indicate that cilomilast has a small volume of distribution (10 to 17 L). Cilomilast is highly bound (99.4%) to plasma proteins, principally to albumin; this binding is independent of concentration up to at least 50 mcg/mL (approximately 30-fold greater than the average C_{max} of 1.7 mcg/mL at 15 mg twice daily).

Metabolism: Cilomilast is extensively metabolized in the liver. The principal routes of metabolism are oxidation (3-hydroxylation on the cyclopentyl ring), acyl glucuronidation, and decyclopentylation, with subsequent glucuronidation or sulfation. The enzyme principally responsible for the oxidative metabolism of cilomilast is CYP2C8. After an oral dose of radiolabeled cilomilast to healthy volunteers, unchanged cilomilast accounted for at least two-thirds of the total circulating drug-related material in plasma. The most abundant metabolite of cilomilast (the *trans*-3-hydroxy metabolite) reaches approximately 10% of the plasma concentrations of cilomilast during repeated dosing of ARIFLO 15 mg twice daily. Because this metabolite has less than 1/10 the potency of cilomilast, its contribution to the therapeutic effects of ARIFLO is negligible.

Cilomilast does not significantly inhibit the human cytochrome P450 (CYP) enzymes 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, or 4A in vitro. Cilomilast (15 mg twice daily) appears to have no significant enzyme-inductive liability based on the lack of effect on urinary markers of CYP3A4 activity (6β-OHC and the ratio of 6β-OHC to free urinary cortisol) at steady state. These properties suggest that cilomilast has little potential to cause or be the target of metabolism-based drug-drug interactions.

Elimination: Cilomilast has a low plasma clearance (1 to 2 L/h) following intravenous administration. After oral administration of radiolabeled cilomilast, more than 90% of a single

10-mg dose was recovered in urine, mostly within 48 hours and almost entirely in the form of identifiable metabolites; only 1% was unchanged cilomilast.

Concentration-Effect Relationships: A population pharmacokinetic analysis was conducted using plasma samples from over 1,000 COPD patients receiving ARIFLO (15 mg twice daily) for 24 weeks. No correlation was found between cilomilast steady-state systemic exposure and efficacy in patients with COPD. There was also no relationship between C_{max} and the incidence of gastrointestinal adverse events in this population.

Special Populations: ***Hepatic Impairment:*** The pharmacokinetics of cilomilast have not been studied in patients with hepatic impairment after administration of ARIFLO 15 mg twice daily. The disposition of cilomilast following a single 10-mg oral dose was compared in subjects with hepatic impairment (moderate or severe) and subjects with normal hepatic function. Compared to healthy subjects, total plasma concentrations of cilomilast (AUC and C_{max}) in subjects with hepatic impairment were unchanged. However, because of reductions in protein binding and intrinsic clearance, unbound concentrations of cilomilast were elevated approximately 2-fold in subjects with moderate hepatic impairment (Child-Pugh Grade B, n = 6) and approximately 5-fold in those with severe hepatic impairment (Child-Pugh Grade C, n = 4). There were no significant differences in the cilomilast elimination half-life between the groups. There are no data in subjects with mild hepatic impairment. ARIFLO is contraindicated in patients with severe hepatic impairment, and should be used with caution in patients with mild or moderate hepatic impairment (see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal Impairment: The disposition of cilomilast following repeated dosing (15 mg twice daily for 7 days) was studied in 29 subjects with varying degrees of renal function. As creatinine clearance (CL_{cr}) decreased, total plasma concentrations of cilomilast ($AUC_{(0-12)}$ and C_{max}) remained unchanged. However, due to reductions in protein binding and intrinsic clearance, unbound cilomilast $AUC_{(0-12)}$ was elevated and the elimination half-life of cilomilast was prolonged. Compared with a typical healthy subject (CL_{cr} = 120 mL/min), regression analysis predicted average increases in unbound $AUC_{(0-12)}$ of 29%, 43%, 65%, and 79% in patients with CL_{cr} values of 80, 60, 30, and 10 mL/min, respectively. Predicted average cilomilast half-lives at these CL_{cr} values were 8.5, 9.6, 11.2, and 12.3 hours, respectively. ARIFLO should be used with caution in patients with severe renal impairment (CL_{cr}<30 mL/min) (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Smokers: The $AUC_{(0-\infty)}$ and elimination half-life of cilomilast following a single 15-mg oral dose were similar in healthy volunteer smokers and non-smokers. No effect of smoking on cilomilast disposition was observed in over 1,000 patients with COPD receiving ARIFLO (15 mg twice daily for 24 weeks) in a population pharmacokinetic analysis. Therefore, no dosage adjustments are required in smokers.

Geriatrics: Following a single oral 10-mg dose, cilomilast $AUC_{(0-\infty)}$ was on average 21% higher in the elderly (65 to 84 years) compared to younger subjects (26 to 43 years). There were no important differences in cilomilast half-life or in vitro plasma protein binding in young and

elderly subjects. In addition, a population pharmacokinetic analysis demonstrated that age did not significantly affect cilomilast disposition in over 1,000 patients with COPD receiving ARIFLO (15 mg twice daily) for 24 weeks. Therefore, no dosage adjustments are required for elderly patients.

Pharmacodynamics: Placebo-controlled studies were conducted to evaluate the potential cardiac effects of cilomilast. These studies included 24–hour Holter tracings that were obtained at baseline, Week 1, and either Week 12 or Week 20 in approximately 200 patients with COPD who received ARIFLO (15 mg twice daily) for up to 6 months. These Holter tracings revealed no increased incidence of cardiovascular events compared to placebo or to baseline in patients with COPD treated with ARIFLO.

Treatment for 7 days with either ARIFLO 15 mg twice daily or placebo had no significant effect on adrenocorticotropic hormone, prolactin, or cortisol concentrations in a study of healthy males and females.

CLINICAL TRIALS

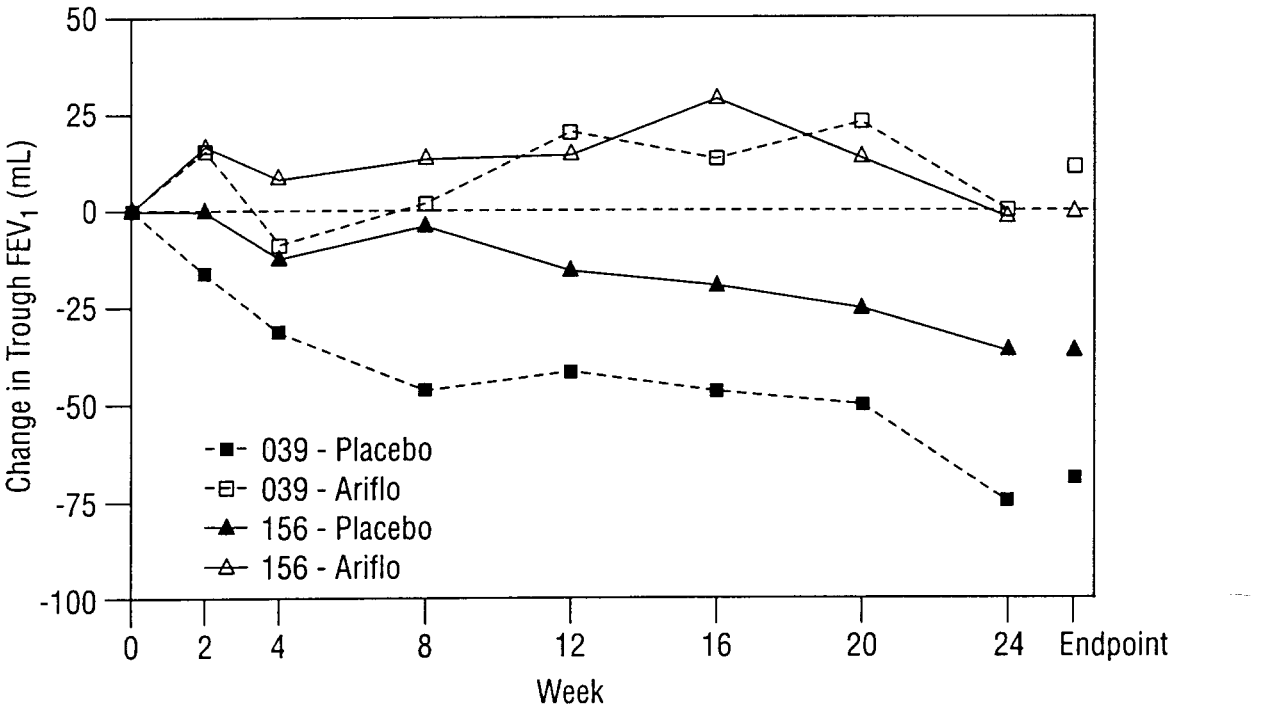
Two large, double-blind, 24-week North American studies were conducted in which ARIFLO 15 mg twice daily was compared to placebo. Patients with a clinical diagnosis of COPD as defined by the American Thoracic Society Guidelines were eligible to participate. In addition, patients had to be poorly responsive to inhaled albuterol. A poor response to albuterol was defined as an improvement in forced expiratory volume in 1 second (FEV_1) of ≤15% or ≤200 mL after albuterol administration. Patients who were using inhaled ipratropium at enrollment were allowed to continue using it (approximately 35% of patients), and all patients were supplied inhaled albuterol for use on an as-needed basis. The primary efficacy measures in these trials were changes from baseline in trough FEV_1 and in St. George's Respiratory Questionnaire (SGRQ) score averaged over 24 weeks. The SGRQ is a validated instrument that measures the impact of diseases of chronic airflow limitation on patient health and well-being. A 4-point change in SGRQ score is considered to be a clinically relevant change (a decrease in SGRQ score reflects an improvement in health status).

In the first study (Study 039), 647 patients were randomized to receive either ARIFLO (n = 431) or placebo (n = 216). At baseline, the mean improvement in FEV_1 after albuterol administration was 7.7% (SD 7.1) for those randomized to ARIFLO and 6.7% (SD 7.6) for the placebo group. The mean age of the patients in this study was approximately 65 years, the mean percent predicted FEV_1 at baseline was approximately 50%, and the mean FEV_1/FVC ratio was 0.51. When averaged over 24 weeks, FEV_1 declined in the placebo group and remained near baseline with ARIFLO resulting in a statistically significant difference in mean change from baseline FEV_1 between treatment groups (difference = 40 mL; 95% CI: 10 to 60 mL; p = 0.002). The difference in mean change from baseline FEV_1 at Endpoint between treatment groups was 80 mL (95% CI: 40 to 120 mL) (see the figure). When averaged over 24 weeks, a statistically significant difference in mean change from baseline SGRQ score between treatment groups was

observed (-4.1 points; 95% CI: –6.0 to –2.2; p<0.001), indicating improvement in health status with ARIFLO.

In the second study (Study 156), 825 patients were randomized to treatment, 418 to ARIFLO and 407 to placebo. At baseline, the mean improvement in FEV_1 after albuterol administration was 8.6% (SD 6.4) in both groups of patients. The mean age of the patients in this study was approximately 64 years, the mean percent predicted FEV_1 at baseline was 50%, and the mean FEV_1/FVC ratio was 0.53. When averaged over the 24 weeks of treatment, FEV_1 values declined in the placebo group and remained near baseline with ARIFLO resulting in a statistically significant difference in mean change from baseline FEV_1 between treatment groups (difference = 20 mL; p = 0.024). The difference in mean change from baseline FEV_1 at Endpoint between treatment groups was 40 mL (95% CI: 10 to 60 mL) (see the figure). When averaged over 24 weeks, the difference in mean change from baseline SGRQ score between treatment groups was -1.9 points (95% CI: -3.5 to –0.35).

Mean Change From Baseline in Trough FEV_1 (Studies 039 and 156)



The clinical effects of ARIFLO in these studies were not affected by patient age, gender, or smoking status.

INDICATIONS AND USAGE

ARIFLO is indicated for the maintenance of lung function (FEV_1) in patients with chronic obstructive pulmonary disease (COPD) who are poorly responsive to albuterol (increase in FEV_1

of ≤15% or ≤200 mL). The efficacy of ARIFLO has not been established in clinical trials beyond 24 weeks.

CONTRAINDICATIONS

ARIFLO is contraindicated in patients who are hypersensitive to cilomilast or to any component of the product.

ARIFLO is contraindicated in patients with severe (Child-Pugh Grade C) hepatic impairment (see CLINICAL PHARMACOLOGY: Special Populations).

WARNINGS

ARIFLO does not produce significant acute effects on FEV_1, and thus should not be used for the treatment of acute bronchospasm. A short-acting bronchodilator should be prescribed for patients who have episodes of acute breathlessness. Do not exceed the recommended dose of ARIFLO or increase the dose to treat acute symptoms or to treat COPD exacerbations.

Due to expected higher exposure to unbound cilomilast, the use of ARIFLO in patients with moderate (Child-Pugh Grade B) hepatic impairment should be undertaken with caution (see CLINICAL PHARMACOLOGY: Special Populations and DOSAGE AND ADMINISTRATION).

PRECAUTIONS

General: Some patients may experience gastrointestinal effects such as nausea, diarrhea, or abdominal pain during treatment with ARIFLO. In the pivotal trials of ARIFLO, the peak gastrointestinal adverse event incidence occurred during the first 4 weeks, after which a gradual decrease in incidence occurred. Gastrointestinal adverse events may resolve with continued treatment.

Concomitant use of ARIFLO with erythromycin has been associated with an increased rate of gastrointestinal adverse events. Concurrent administration of these agents should be used with caution (see PRECAUTIONS: Drug Interactions).

ARIFLO should be used with caution in patients with mild hepatic impairment and in patients with severe renal impairment (see CLINICAL PHARMACOLOGY: Special Populations and DOSAGE AND ADMINISTRATION).

Due to findings in animals (see ANIMAL TOXICOLOGY), patients presenting with serious gastrointestinal complaints, or bloody or black stools should undergo medical evaluation.

Information for Patients: Patients being treated with ARIFLO should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

1. Patients should take ARIFLO regularly, even during periods when they are having few or no symptoms. The patient should not increase the prescribed dosage. If the condition worsens, the patient should contact the physician.
2. If a dose of ARIFLO is missed by more than 4 hours, the patient should omit that dose and take the next scheduled dose when it is due. If fewer than 4 hours have elapsed, the patient

may take the missed dose and then take the next dose at its scheduled time. Missed doses should not be made-up by doubling the next dose.

3. Patients receiving ARIFLO should be instructed not to decrease the dose or stop taking other medications unless instructed by a physician.
4. ARIFLO is not meant to relieve acute COPD symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist such as albuterol (the physician should prescribe such medication for the patient and instruct the patient in how to use it).
5. The physician should be notified immediately if any of the following situations occur, which may be a sign of worsening COPD:
   - Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
   - Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
   - More breathlessness than usual
6. Patients should be advised regarding adverse effects that may occur during therapy including nausea, diarrhea, and abdominal pain.
7. It is recommended to take ARIFLO with food.
8. Patients who are pregnant or nursing should contact the physician about the use of ARIFLO.
9. Concurrent use of erythromycin and ARIFLO should be undertaken with caution due to an increased risk of gastrointestinal adverse events.
10. Patients should be advised to contact their doctor promptly if they have serious gastrointestinal complaints, or bloody or black stools.

Drug Interactions: Cilomilast does not significantly inhibit the human cytochrome P450 (CYP) enzymes 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, or 4A in vitro. Based on the lack of effect on urinary markers of CYP3A4 activity (6β-OHC and the ratio of 6β-OHC to free urinary cortisol) at steady state, cilomilast (15 mg twice daily) has no significant enzyme inductive liability.

Because cilomilast is highly bound (>99%) to plasma proteins (principally albumin), there is a theoretical potential for drug-drug interactions based upon protein binding displacement. However, no changes in the pharmacodynamic effects of warfarin were noted with the concomitant administration of cilomilast (see Warfarin below).

As outlined below, ARIFLO (15 mg) has been coadministered with warfarin, theophylline, digoxin, erythromycin, and MAALOX Plus® in healthy volunteers in drug interaction studies. In each case, no significant pharmacokinetic interaction was observed. However, coadministration of ARIFLO with erythromycin was associated with an increased incidence of gastrointestinal adverse events (see Erythromycin below).

Warfarin: ARIFLO (15 mg twice daily) was administered concomitantly with warfarin (at therapeutic doses) to 17 healthy volunteers for 7 days. ARIFLO had no clinically relevant effects on the steady-state international normalized ratio values established during administration of warfarin alone.

Theophylline: ARIFLO (15 mg twice daily) was administered concomitantly with theophylline (at therapeutic doses) to 15 healthy volunteers for 4 days. No clinically relevant changes in the steady-state pharmacokinetics, safety, or tolerability of theophylline were observed during coadministration with ARIFLO when compared to theophylline administered alone. The steady-state pharmacokinetics of cilomilast were also unaffected by theophylline coadministration. The coadministration of ARIFLO with theophylline has not been evaluated in COPD patients.

Digoxin: ARIFLO (15 mg twice daily) was administered concomitantly with digoxin (0.375 mg once daily) to 13 healthy volunteers for 14 days. No clinically relevant changes in the steady-state pharmacokinetics, safety, or tolerability of digoxin were observed during coadministration with ARIFLO when compared to digoxin administered alone. The steady-state pharmacokinetics of cilomilast were also unaffected by digoxin coadministration.

Erythromycin: An increased rate of adverse events (nausea, diarrhea, abdominal pain) was noted in a small number of healthy subjects in which ARIFLO (15 mg twice daily) and erythromycin (500 mg 3 times daily) were initiated simultaneously compared to administration of either drug alone. In a subsequent study involving 31 healthy volunteers, erythromycin (250 or 500 mg 3 times daily) was introduced after 5 days of dosing with either ARIFLO (15 mg twice daily) or placebo alone. Although this method of administration was better tolerated than simultaneous initiation of therapy, there was still a higher rate of gastrointestinal adverse events in subjects who received both ARIFLO and erythromycin compared with those who received erythromycin alone. No clinically relevant changes in the steady-state pharmacokinetics of cilomilast were observed following the addition of erythromycin, nor did ARIFLO markedly affect the steady-state pharmacokinetics of erythromycin. However, due to the increased risk of gastrointestinal adverse events, the concomitant use of ARIFLO and erythromycin should be undertaken with caution (see PRECAUTIONS: General).

Aluminum/Magnesium Hydroxide Antacid: In a study involving 21 healthy volunteers, coadministration of the antacid MAALOX Plus with a single 15-mg oral dose of ARIFLO, either under fed or fasted conditions, did not alter the bioavailability of cilomilast.

Other Drug Interaction Studies: Prednisolone: ARIFLO (10 mg twice daily) was administered concomitantly with oral prednisolone (10 mg once daily) for 7 days to 12 healthy volunteers. No significant changes in the steady-state pharmacokinetics of prednisolone were observed.

Inhaled albuterol: Fifteen healthy volunteers received inhaled albuterol after 5 days of treatment with either ARIFLO (10 mg twice daily) or placebo. ARIFLO had no effect on the pharmacodynamic response to albuterol as measured by vital signs, Holter ECG, and hand tremor.

Clinical Trial Experience: In the large, 24-week efficacy trials, ARIFLO (15 mg twice daily) was used concomitantly with inhaled ipratropium and with inhaled albuterol. In long-term, open-label studies, ARIFLO was used with long acting $beta_2$-agonists (salmeterol, formoterol), inhaled corticosteroids (triamcinolone, fluticasone, budesonide, beclomethasone, flunisolide),

and oral corticosteroids (prednisone, prednisolone). The concomitant use of these medications did not appear to increase the incidence, or influence the pattern of adverse events associated with ARIFLO.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year carcinogenicity study in CD-1 mice, an increased incidence of mammary adenoma/adenocarcinoma was noted at 100 mg/kg/day in female mice only. This was not observed at doses of 10 or 30 mg/kg/day (up to 18 times the expected human clinical exposure to unbound cilomilast at a 15-mg twice-daily dose). Mammary adenomas/adenocarcinomas occurred at a dose similar to that causing pseudopregnancy, a condition associated with the induction of mammary tumors in mice. Since there is no human analogy of pseudopregnancy, these tumors are considered of unlikely clinical relevance.

In a 2-year carcinogenicity study in Sprague Dawley rats at doses of 2, 5, and 20 mg/kg/day (up to 9 times the expected human clinical exposure to unbound cilomilast), there was no evidence of tumorigenicity.

Cilomilast was not mutagenic in the Ames, mouse lymphoma, or mouse micronucleus assay and did not induce unscheduled DNA synthesis in an in vivo/in vitro rat liver assay. In a human lymphocyte assay, chromosomal damage was observed at concentrations ≥1,200 mcg/mL. These concentrations also resulted in significant toxicity (>50%) to cultured human lymphocytes. Neither chromosomal damage nor significant cytotoxicity was observed at concentrations ≤950 mcg/mL.

Cilomilast had no effect on fertility of male or female rats at doses up to 40 mg/kg/day (this represents 3 and 10 times the expected human clinical exposure based on unbound cilomilast AUCs obtained in male and female rats, respectively).

Cilomilast was associated with testicular degeneration in rats when administered at vasculotoxic doses of ≥40 mg/kg/day. This was not observed at a dose of 30 mg/kg/day (greater than 13 times the expected human clinical exposure to unbound cilomilast). The effect of cilomilast on semen characteristics was examined in a placebo-controlled study involving approximately 100 normal young (18 to 35 years) volunteers. Subjects received either ARIFLO or placebo for 84 days, followed by an 84-day follow-up period. Semen samples were obtained at 3 timepoints during treatment and 3 timepoints during follow-up. No clinically relevant effects were observed at any timepoint for sperm count, morphology, or motility.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. In an embryo-fetal development study in female rats, oral administration of cilomilast at a dose of 40 mg/kg/day resulted in delayed fetal skeletal ossification and maternal toxicity. In an embryo-fetal development study in female rabbits, oral administration of cilomilast resulted in embryo-fetal lethality and maternal toxicity at a dose of 45 mg/kg/day. Embryo-fetal effects were not detected in rats or rabbits given doses that were not maternally toxic (≤5 mg/kg/day; 1.5 or 1.4 times, respectively, the expected human clinical exposure to unbound cilomilast).

In an oral pre- and post-natal development study in rats, cilomilast doses of 0.2, 5, or 20 mg/kg/day had no adverse effect on pregnancy, parturition, or lactation. Offspring from dams

330 treated at 20 mg/kg/day had lower body weight during the postweaning period, but development
331 was otherwise normal. Cilomilast was without pre- or post-natal effects in rats at doses of
332 ≤5 mg/kg/day. There are no adequate and well-controlled studies in pregnant women. ARIFLO
333 should be used during pregnancy only if the potential benefit justifies the potential risk to the
334 fetus.
335 **Nursing Mothers:** Cilomilast and/or its metabolites are excreted into the milk of lactating rats.
336 It is not known if cilomilast or its metabolites are excreted into human milk. Because many drugs
337 are excreted in human milk, caution should be exercised when ARIFLO is administered to a
338 nursing woman.
339 **Pediatric Use:** The safety and effectiveness of ARIFLO in pediatric patients have not been
340 established.
341 **Geriatric Use:** Of the 1,931 patients treated with ARIFLO in the Phase III COPD clinical
342 studies, 1,028 (53%) were 65 years of age and older and 219 (11%) were 75 years of age or
343 older. No overall differences in safety or efficacy were observed between these subjects and
344 younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

345 **ADVERSE REACTIONS**

346 ARIFLO was administered to 1,792 patients with COPD in trials of 24 weeks' duration. The
347 majority (53%) of the patients with COPD in the large controlled trials of ARIFLO were
348 65 years of age or older and 71% were male. The most common adverse events reported in these
349 studies were nausea, diarrhea, and abdominal pain.

350 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
351 observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of
352 another drug and may not reflect the rates observed in practice. The adverse reaction information
353 from clinical trials does, however, provide a basis for identifying the adverse events that appear
354 to be related to drug use and for approximating rates.

355 Adverse events reported by >5% of patients treated with ARIFLO in the 24-week pivotal
356 efficacy studies and that were more common with ARIFLO than placebo are shown in the table.
357 Approximately 18% of patients discontinued therapy with ARIFLO due to adverse events
358 compared with 12% of patients receiving placebo.
359

Adverse Events Reported by >5% of Patients Treated With ARIFLO in 24-Week COPD Clinical Trials

Adverse Event	ARIFLO N = 1,792	Placebo N = 1,091
Nausea	16%	5%
Diarrhea	14%	8%
Abdominal pain	12%	7%
Headache	8%	7%
Dyspepsia	7%	3%
Vomiting	6%	2%

The following adverse events were reported by ≥1% and ≤5% of patients receiving ARIFLO, and were reported at an equal frequency or at a greater rate than in placebo patients:

Body as a Whole: Rash, fatigue, injury, viral infection.

Central and Peripheral Nervous System: Tremor, asthenia, pain, dizziness.

Gastrointestinal: Gastroenteritis, gastroesophageal reflux, melena, anorexia, flatulence.

Hematologic: Leukocytosis.

Metabolic and Nutritional: Hyperkalemia, weight decreased.

Musculoskeletal: Arthralgia, back pain.

Psychiatry: Depression, anxiety, insomnia.

Urinary System: Hematuria.

Of the patients who participated in the pivotal clinical efficacy trials, 1,078 enrolled in open-label extension studies of ARIFLO, 796 of whom received ARIFLO for 18 months or longer. The adverse event profile of ARIFLO in these long-term studies was similar to that observed in the 24-week pivotal efficacy studies.

OVERDOSAGE

Doses greater than recommended may be associated with a higher incidence of nausea and vomiting. In the event of overdose, treatment would include discontinuation of ARIFLO, and initiation of appropriate supportive treatment as dictated by the patient's clinical status. Because cilomilast is highly protein-bound, hemodialysis would not be expected to significantly enhance the removal of cilomilast from the blood. Activated charcoal has been shown to block the oral absorption of cilomilast.

DOSAGE AND ADMINISTRATION

The recommended dose of ARIFLO is 15 mg twice daily. It is recommended that ARIFLO be taken with food.

No dosage adjustments are required for elderly subjects or for smokers.

Therapy with ARIFLO should be continued during acute exacerbations of COPD. Inhaled albuterol should be used for relief of acute breathlessness.

Patients With Hepatic Impairment: ARIFLO is contraindicated in patients with severe (Child-Pugh Grade C) hepatic impairment (see CLINICAL PHARMACOLOGY: Special Populations and CONTRAINDICATIONS). ARIFLO should be used with caution in patients with moderate (Child-Pugh Grade B) hepatic impairment because these subjects may have higher exposures to unbound cilomilast (see CLINICAL PHARMACOLOGY: Special Populations and WARNINGS). Since there are no data on patients with mild hepatic impairment, caution is also warranted in these patients.

Patients With Renal Impairment: ARIFLO should be used with caution in patients with severe renal impairment (creatinine clearance <30 mL/min) because these subjects may have higher exposures to unbound cilomilast (see CLINICAL PHARMACOLOGY: Special Populations and PRECAUTIONS: General).

HOW SUPPLIED

ARIFLO Tablets, 15 mg, are pale yellow, octagonal, film-coated TILTAB® tablets debossed with "GSK" on one side "3125" on the other in bottles of 60 tablets (NDC 0007-3125-18) and unit-dose packages of 100 tablets (NDC 0000-0000-00).

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

ANIMAL TOXICOLOGY

Medial necrosis was observed in splanchnic arteries in mice and rats administered cilomilast doses ≥200 mg/kg/day and ≥30 mg/kg/day, respectively. The no-effect dose in rats was 7.2 times the human exposure based on AUCs for unbound cilomilast and in mice was 119 times the estimated human exposure. This effect was not observed in rabbits (treated for 1 month at 60 mg/kg/day) or monkeys (treated for up to 1 year at 10 mg/kg/day) at systemic exposures which were 7 times the human exposure based on AUCs for unbound cilomilast. The clinical relevance of these findings is not known.

GlaxoSmithKline
Research Triangle Park, NC 27709

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